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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/081,817	02/22/2002	Kornelia Polyak	00530-094001/ DFCI#689	3070

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FISH & RICHARDSON PC
225 FRANKLIN ST
BOSTON, MA 02110

EXAMINER	
NICKOL, GARY B	

ART UNIT	PAPER NUMBER
1642	16

DATE MAILED: 11/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/081,817	POLYAK ET AL.	
	Examiner	Art Unit	
	Gary B. Nickol Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *02 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *23-46* is/are pending in the application.

4a) Of the above claim(s) *25-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *23,24 and 35-46* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Response to Amendment

The Amendment filed September 2, 2003 (Paper No. 15) in response to the Office Action of March 31, 2003 is acknowledged and has been entered.

Claims 1-22 are cancelled.

Claims 25-34 are withdrawn from further consideration by the examiner under 37 CFR 1.142(b) as being drawn to non-elected inventions.

Claims 36-46 have been added.

Claims 23-24, and 35-46 are currently under consideration.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

Objection Maintained:

The specification remains objected to because it contains an embedded hyperlink and/or other form of browser-executable code. Applicants amended (Response filed 09/02/03, Page 2) the specification to remove the hyperlink on page 4. However, there are hyperlinks remaining. For example, see page 14, line 20. Applicant is requested to remove all embedded hyperlinks and/or other form of browser-executable codes. See MPEP § 608.01.

Rejections Maintained:

Claims 23-24 remain rejected and Claims 44-46 are rejected as vague and indefinite for reciting the term HIN-1 in association with a promoter region as the sole means of identifying said region for the reasons of record (Paper No. 13, page 3). It is noted that applicants have amended Claim 23 to recite the promoter region and the first twelve nucleotides of SEQ ID NO:3. However, the claims remain indefinite because the claims still recite the HIN-1 promoter region in the absence of a unique identifier. This rejection can be obviated by amending the claims to incorporate the subject matter of new claims 42 or 43.

New Rejections:

Claims 23-24, and 35-46 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are vague and indefinite because Claim 23 recites "wherein a *high* degree of methylation of the C residues is an indication that the test cell is a cancer cell". The phrase "a high degree" is a relative term that is not defined by the claim. Furthermore, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. This rejection can be obviated by amending the claims to incorporate a comparison to a normal standard, i.e. "wherein a higher degree of methylation of the C residues in the test sample as compared to a corresponding normal sample of cells is an indication that the test cells are cancerous". *Applicant is reminded that no new matter may be incorporated into the claimed subject matter. Further, with respect to newly added or amended claims, applicant should show*

support in the original disclosure for the new or amended claims. See MPEP §714.02 and § 2163.06.

Claims 38-43 are further rejected under 35 USC 112, 2nd paragraph. Claims 38-43 recite the term "the segment". There is insufficient antecedent basis for this terminology from which claims 38-43 depend.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 38-41 are rejected under 35 USC 112, first paragraph, as the specification does not contain a written description of the claimed invention. The limitation of "nucleotides 1 to 252 of SEQ ID NO:19" and "nucleotide 229 to nucleotide 551 of SEQ ID NO:19" does not appear to have clear support in the specification and the claims as originally filed. Applicants point out (Response filed 09/02/03, Page 6) that support for the new claims encompassing claims 38-41 are supported by the specification on pages 26-28, Example 4, and the Sequence Listing. The suggested support is not found persuasive because no specific support could be found as referenced by Applicants. Further, the Sequence Listing indicates that SEQ ID NO:19 comprises 551 nucleotides and there is nothing in the specification to suggest using nucleotides 1 to 252 of SEQ ID NO:19 or nucleotide 229 to nucleotide 551 of SEQ ID NO:19 as claimed.

If applicant should disagree with this rejection, applicant should submit evidence pointing to the serial number, page and line where support can be found for the disputed terminology.

Claims 23, and 35-46 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of diagnosing breast cancer, the method comprising: (a) providing a test sample of potentially cancerous breast cells

(b) providing a sample of corresponding normal breast cells

(c) determining in the samples the degree of methylation of one or more C residues in a HIN-1 promoter region comprising (i) SEQ ID NO:19 and (ii) the first twelve nucleotides of SEQ ID NO:3, wherein the C residues are C residues in CpG sequences, and

wherein a higher degree of methylation of the C residues in the test sample as compared to the corresponding normal breast cells is an indication that the test breast cells are cancerous,

----does not reasonably provide enablement for the broadly claimed invention. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *Ex parte* Forman, 230 USPQ 546 (BPAI 1986). They include the nature of the invention, the state of the prior art, the relative skill of those in the art, the amount of direction or guidance disclosed in the specification, the presence or absence of working examples, the predictability or unpredictability of the art, the breadth of the claims, and the quantity of experimentation which would be required in order to practice the invention as claimed.

The claims are broadly drawn to a method of diagnosis in a test cell comprising determining the degree of methylation of one or more C residues in a nucleotide sequence consisting of the HIN-1 promoter region and the first twelve nucleotides of SEQ ID NO:3 wherein the C residues are C residues in CpG sequences, and wherein a high degree of methylation of the C residues is an indication that the test cell is a cancer cell.

This includes enabling the diagnosis of any and all test cells to determine if a cancer is present including, but not limited to, test cells from lung cells, prostate cells, pancreatic cells, gastrointestinal cells, and skin cells (Claim 35) by determining a high degree of methylation. This further includes determining the degree of methylation in any and all promoter regions solely defined by the term HIN-1.

The specification teaches (page 38, lines 14+ and Figure 6A, 6C) that a methylation specific PCR (MSP) assay was developed in order to analyze the methylation status of the human HIN-1 (hHIN) promoter region in primary breast tissues. Indeed, when compared to three independent normal breast tissues, the degree of methylation in the breast cancer tissues and breast cancer cell lines is higher than the control or normal breast tissue. The specification further teaches the approximate degree of methylation (bisulfite treated genomic DNA) in the hHIN-1 promoter region and portions of the hHIN-1 coding region in test pancreatic (ASCP), prostate (PC3 and LNCP) and lung cancer cells (Figure 6 A). The specification further teaches (page 9, line 8) a nucleotide sequence immediately 5' of the coding sequence for the hHIN-polypeptide wherein said nucleotide sequence is a promoter region of SEQ ID NO:19.

However, one cannot extrapolate the teachings of the specification to the scope of the claims because the claims are broadly drawn to diagnosing any and all cancers (including, but

not limited to lung, prostate, pancreatic, gastrointestinal cells, and skin cancer) by determining a high degree of methylation, and applicant has not enabled the diagnosis of all of these types of cancer because it has not been shown that a relatively high degree of methylation in the hHIN-1 promoter region in any and all potentially cancerous cells would be indicative of cancer. While those of relative skill in the art can appreciate that certain epigenetic events may contribute to the silencing of a particular gene via hypermethylation, such events do not reasonably extrapolate to the *diagnosis* of any and all cancers. In this particular case, the degree of methylation in non-breast cancerous cells can only be interpreted as relative. For example, the specification (page 37, line 27) teaches that a "moderate" level of the hHIN-1 promoter region was methylated in DNA from a pool of four lung carcinoma tissue samples. What is a moderate level? In other non-breast cancerous cells, the degree of methylation is "high"; however, it is not clear how high the methylation must be to reasonably predict the presence of cancer in non-breast tissue. Is it two, four, or twenty C residues that must be methylated? Further, with regards to non-breast cancerous cells, there is no comparison of the methylation status in control and or non-cancerous cells. Thus, there is no requisite for determining what exactly constitutes a high level of methylation, which in turn, would constitute a predictable diagnosis of cancer. The only non-breast cells in the test are already cancerous, so it would stand to reason that other factors, beyond the status of methylation in the promoter region, may give rise to the cancerous state. Indeed, the specification teaches (page 38, line 11) that methylation is at least partially responsible for the loss of hHIN-1 expression, and that (page 38, line 26) other factors might be responsible for silencing hHIN-1 such as age-dependent differences. Reasonable correlation must exist between the scope of the claims and scope of enablement set forth, and the

specification does not provide reasonable guidance for diagnosing any and all cancers by determining the level of methylation in the hHIN-1 promoter region which would predictably be indicative of the cancerous state.

Additionally, one cannot extrapolate the teachings of the specification with the scope of the claims because the claimed method (pertaining to Claims 23-24, 35, 44-46) broadly reads on determining the degree of methylation in *any* nucleotide region labeled as a HIN-1 promoter region, and it would not be expected that any and all nucleotide regions would predictably diagnose the presence of cancer. When given the broadest reasonable interpretation, the promoter region clearly encompass a variety of species including full-length cDNAs, genes and protein coding regions. Clearly, it would be expected that a substantial number of the polynucleotide molecules encompassed by the claims **would not** share either structural or functional properties with HIN-1 promoter regions. Hence, only a promoter region comprising SEQ ID NO:19 meets the scope of enabled subject matter.

Thus, in view of the above, it would require undue experimentation to practice the method as broadly claimed.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Gary B. Nickol Ph.D. whose telephone number is 703-305-7143. The examiner can normally be reached on M-F, 8:30-5:00 P.M..

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Anthony Caputa can be reached on 703-308-3995. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Gary B. Nickol, Ph.D.
Examiner
Art Unit 1642

GBN
November 11, 2003